REMARKS

Status of the Claims:

Upon entry of the amendment, claims 26-49, 51-58 and 61-67 are pending in this application and claims 31, 44-49, 61 and 62 are withdrawn. Applicants have amended the specification to correct various typographical errors.

Claim 50 is canceled herein without prejudice or disclaimer of Applicants' right to pursue the canceled subject matter in this or a related application. Claims 26-28, 30, 35, 36, 51-58, 63 and 65 are amended herein.

Support for the amendment to the claims is supported throughout the specification as originally filed, for example, page 27, lines 3-16; page 6, line 23; page 27, line 6; page 35, lines 4-6; and page 38, line 29 through page 39, line 10 of the specification as originally filed.

Applicants respectfully submit that no new matter is introduced.

Claims 26-30, 32-43, 50-58 and 63-67 are rejected. Claims 25-30, 33-43, 50, 58, 63, 64 and 67 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 6,165,193 to Greene, Jr. et al. ("Greene"). Claims 32, 51-53 and 65 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Greene. Claims 54, 55 and 66 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greene in view of U.S. Patent No. 6,784,273 to Spaans et al. ("Spaans"). Claims 56 and 57 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greene in view of U.S. Patent No. 6,231,590 to Slaikau et al. ("Slaikeu").

In view of the above amendments and following remarks, it is respectfully submitted that all of the presently pending claims are allowable.

Specification:

The Examiner objects to the specification because there allegedly are errors in the "Brief Description of the Drawings" section. In view of the foregoing amendments to the specification, Applicants respectfully request withdrawal of this objection.

Response to Anticipation Rejection Under 35 U.S.C. §102(b):

Claims 26-30, 33-43, 50, 58, 63, 64 and 67 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 6,165,193 to Greene, Jr. et al. ("Greene").

A rejection of claims as anticipated under 35 U.S.C. §102(b) requires a showing that each and every claim limitation be identically disclosed in the applied reference. If even one claim limitation is not disclosed in the reference, the reference does not anticipate the claim.

The Office Action relies on element 20 in Figure 2 of the Greene reference as a basis for "a polymeric matrix implant." (Office Action, p.3). Applicants' amended claim 63 now recites "a reticulated elastomeric matrix." Similarly, independent claim 67 recites "a biodurable reticulated elastomeric matrix." As explained below, the Office Action continues to ignore and fails to show that the cited reference discloses at least one implant comprising a **reticulated elastomeric** matrix as required by Applicants' claims 63 and 67.

As discussed in Applicants' response of September 13, 2007, the specification of the present application provides that a reticulated matrix possesses a microstructure or interior structure comprising "inter-connected open pores bounded by configuration of the struts and intersections that constitute the solid structure." (Specification, page 27, lines 12-15). Applicants stated that "[t]he continuous interconnected void phase is the principle feature of a reticulated structure." (Specification, page 27, lines 15-16). Moreover, the presence of inter-connected,

reticulated open pores form fluid passageways or fluid permeability that allow for fluid access all through and to the interior of the matrix. (See Specification, page 27, lines 22-24).

Greene does not contemplate a **reticulated** matrix having a microstructure comprising **inter-connected open pores** bounded by configuration of the struts and intersections that constitute the solid structure. Greene discloses an implant having "a hydrophilic, **macroporous**, polymeric, **hydrogel** foam material," which exhibits different physical properties, and provides a completely different type of polymer and macroscopic structure as compared to a **reticulated elastomeric** matrix recited by Applicants' claims. (*See* Greene, col. 3, lns. 50-53).

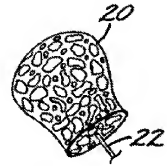

FIG. 2

It appears that Figure 2 of the Greene reference, which is reproduced above, shows a hydrogel having irregularly-shaped and irregularly-sized "macroscopic" pores. Greene does not teach or suggest a **continuous interconnected void phase** or fluid passageways or fluid permeability providing fluid access all through and to the interior of a matrix. Accordingly, Applicants respectfully submit that Greene does not provide for a "reticulated elastomeric matrix" as recited by claims 63 and 67.

As would be understood by one skilled in the art, an elastomeric matrix, by definition, comprises a polymer that possesses elastic properties, that is, the ability to reversibly deform under stress and return to its original shape once the stress is removed. Applicants'

specification is also consistent with this well-known definition for an elastomeric matrix. In particular, the specification defines the term elastomeric as "...that they can be compressed and can resiliently recover to substantially the pre-compression state." (Specification, page 28, lines 5-6). The elastic properties of the matrix provide a mechanism for the implant to expand "from a first configuration to a second configuration, the second configuration being larger than the first configuration."

Greene also does not teach or suggest an implant comprising an **elastomeric** matrix. In contrast, Greene requires that the implant be compressed and be set "in its compressed configuration by heating and/or drying." (Greene, col. 7, lns. 27-28). A continuing compressive force is not required to maintain the hydrogel disclosed by Greene in a compressed configuration. An elastomer does not and cannot be maintained in a compressed configuration solely by heating and/or drying. By definition, the elastomer must be able to substantially recover to its original shape once the stress (*e.g.*, compression) is removed.

Moreover, Greene discloses that its implant expands by "hydrophilic hydration of the implant material" and/or "from the filling of its pores with blood." (Greene, col. 8, 22-27). Specifically, if the implant was formed from "a non-hydrophilic material, its expansion [would be] due to the latter mechanism **only**." (Greene, col. 8, lns. 26-27)(*emphasis added*.). Greene restricts its disclosure to implants comprising materials that only expand due to the disclosed mechanisms. Greene does not contemplate any alternative mechanisms for expanding an implant. Greene's hydrogel cannot and does not resiliently recover to substantially the pre-compression state without the addition of external forces (*e.g.*, fluid pressure). Applicants' claims recite an implant comprising a reticulated elastomeric matrix, which is capable of substantially restoring its original shape without absorbing aqueous fluids or filling its pores with

blood or any other liquid. Accordingly, the implant of Greene is not what is called for in the amended claim language of the present application.

Therefore, Applicants respectfully submit that claims 63 and 67, and claims 27-30, 33-43, 58, and 64, which depend therefrom, cannot be anticipated by Greene. For at least the foregoing reasons, Applicants respectfully request withdrawal of all §102(b) rejections over Greene.

Response to Obviousness Rejection Under 35 U.S.C. §103:

Claims 32, 51-53 and 65 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Greene. Claims 54, 55 and 66 also rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greene in view of U.S. Patent No. 6,784,273 to Spaans et al. ("Spaans"). Claims 56 and 57 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greene in view of in view of U.S. Patent No. 6,231,590 to Slaikau et al. ("Slaikeu").

A rejection under 35 U.S.C. §103(a) requires the establishment of a *prima facie* case that the claimed subject matter, including all claim elements, would have been obvious to a person having ordinary skill in the art on the basis of either a single prior art reference or more than one reference properly combined. As no such *prima facie* case has been established for these claims, Applicants respectfully traverse these rejections, as set forth more fully below.

For at least the reasons discussed above, Greene fails to teach or suggest all of the claim elements of Applicants' claims. As demonstrated below, the secondary references cited by the Examiner, Spaans and Slaikeu, do not cure the deficiencies of Greene.

Spaans describes a biomedical polyurethane based on diisocyanate linked polyester polymer and diol components, said diol component having a uniform block length.

Spaans does not teach or suggest either a device for treating a vascular malformation or a reticulated elastomeric matrix as recited by Applicants' claims.

Slaikeu describes a vaso-occlusion device, such as a coil, at least partially coated with a bioactive agent, a collagenous material, or a collagenous coating optionally containing or coated with other bioactive agents. Slaikeu does not contemplate treating a vascular malformation with a device comprising at least one implant comprising a biodurable reticulated matrix being expandable from a compressed configuration sized for delivery into the internal volume of the vascular malformation to an expanded configuration.

Additionally, Applicants respectfully submit that Greene cannot be modified to include a reticulated elastomeric matrix as recited by Applicants' claims. According to MPEP 2143.01, VI, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." One of the principles of operation of the hydrogel implant disclosed by Greene is that the implant be compressed and be set "in its compressed configuration by heating and/or drying." (Greene, col. 7, lns. 27-28). As discussed above, an elastomer cannot be "set" in a compressed configuration by heating and/or drying. To compress the implant of the present invention comprising a reticulated elastomeric matrix, there must be a continuing application of a compressive force. Absent the compressive force, the elastic properties of the matrix would be capable of substantially restoring the implant to its original shape. Therefore, to maintain the implant of the present invention in a compressed configuration, there must be a substantial redesign of the implant of Greene, utilizing different principles under which the implant is maintained in a compressed configuration.

Furthermore, with respect to claims 54, 55 and 66, Spaans does not teach or suggest a biodurable elastomeric matrix as required by Applicants' claims 54, 55 and 66 and defined by the specification as:

> The biodurable elastomeric matrices forming the scaffold do not exhibit significant symptoms of breakdown, degradation, erosion or significant deterioration of mechanical properties relevant to their use when exposed to biological environments and/or bodily stresses for periods of time commensurate with the use of the implantable device such as controlled release or elution of pharmaceutically-active agents, e.g., a drug, or other biologically useful materials over a period of time. In one embodiment, the desired period of exposure is to be understood to be at least 29 days." (Specification, page 29, lines 12-24).

The Office Action states that Spaans "teaches a polymeric foam for implants may be polyurethane with an isocyanate component and a polycarbonate component." (Office Action, page 4). According to Spaans, its invention is directed to a "biomedical polyurethane based on diisocyanate linked **polyester** polymer and diol components, said diol component having a uniform block-length." (Spaans, Abstract). Spaans makes merely a single passing mention of "polycarbonate" as an exemplary soft segment for polyurethanes and does not teach or suggest biodurable polymers. (Spaans, col. 2, line 52). All of the exemplary embodiments described in Spaans are directed to polyurethane **polyester** polymers. The only polycarbonate polymers described by Spaans are **polyester** polymers having trimethylene carbonate units. (Spaans, col. 4, lines 40-43). One of ordinary skill in the art would understand that the polyurethane foams made from polyester backbones, including those having polycarbonate units, as described by Spaans, are susceptible to degradation when exposed to biological environments and would not provide a **biodurable** matrix. As discussed in Applicants' response of September 13, 2007, a paper by Stokes et al. published in 1995 recognized that "[p]olyester polyurethanes, such as

those used until only recently as coverings for implanted breast prostheses are subject to hydrolytic degradation." Stokes et al., "Polyurethane Elastomer Biostability," Journal of Biomaterials Applications, Vol. 9, 321-354, 350 (1995). As another example, a paper by Middleton et al. published in March 1998 titled "Synthetic Biodegradable Polymers as Medical Devices," specifically identified poly(glycolide-co-trimethylene carbonate), which is a polyester having trimethylene carbonate units, as a biodegradable polymer. Middleton et al., "Synthetic Biodegradable Polymers as Medical Devices," Medical Plastics and Biomaterials, 30, (March 1998)(accessible at http://www.devicelink.com/mpb/archive/98/03/002.html)(Exhibit A). Accordingly, Applicants respectfully submit that Spaans is of no relevance to claims 54, 55 and 66.

For at least the reasons discussed above, Applicants respectfully submit that Greene in view of Spaans and/or Slaikeu do not teach or suggest Applicants' invention as recited by claims 32, 51-57, 65-66 . Therefore, Applicants respectfully request withdrawal of all §103 rejections.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request withdrawal of the rejections of claims and allowance of this application. In the event that a telephone conference would assist in the examination of this application, Applicants invite the Examiner to contact the undersigned at the number provided.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 14596.105002. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 14596.105002.

Respectfully submitted,
King & Spalding, LLP

Dated: June 6, 2008

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EXHIBIT A

Medical Device Link.

The Online Information Source for the Medical Device Industry

Medical Plastics and Biomaterials Magazine
MPB Article Index

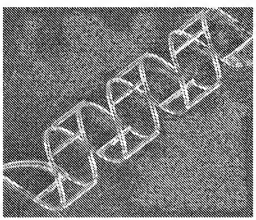
Originally published March 1998

MATERIALS

Synthetic Biodegradable Polymers as Medical Devices

John C. Middleton and Arthur J. Tipton

In the first half of this century, research into materials synthesized from glycolic acid and other α-hydroxy acids was abandoned for further development because the resulting polymers were too unstable for long-term industrial uses. However, this very instability—leading to biodegradation—has proven to be immensely important in medical applications over the last three decades. Polymers prepared from glycolic acid and lactic acid have found a multitude of uses in the medical industry, beginning with the biodegradable sutures first approved in the 1960s. Since that time, diverse products based on lactic and glycolic acid—and on other materials, including poly (dioxanone), poly(trimethylene carbonate) copolymers, and poly (ε-caprolactone) homopolymers and copolymers—have been accepted for use as medical devices. In addition to these approved devices, a great deal of research continues on polyanhydrides, polyorthoesters, polyphosphazenes, and other biodegradable polymers.



A biodegradable intravascular stent prototype is molded from a blend of polylactide and trimethylene carbonate. Photo: Cordis Corp. Prototype Molded by Tesco Associates, Inc.

Why would a medical practitioner want a material to degrade? There may be a variety of reasons, but the most basic begins with the physician's simple desire to have a device that can be used as an implant and will not require a second surgical intervention for removal. Besides eliminating the need for a second surgery, the biodegradation may offer other advantages. For example, a fractured bone that has been fixated with a rigid, nonbiodegradable stainless implant has a

tendency for refracture upon removal of the implant. Because the stress is borne by the rigid stainless steel, the bone has not been able to carry sufficient load during the healing process. However, an implant prepared from biodegradable polymer can be engineered to degrade at a rate that will slowly transfer load to the healing bone. Another exciting use for which biodegradable polymers offer tremendous potential is as the basis for drug delivery, either as a drug delivery system alone or in conjunction to functioning as a medical device.

Polymer scientists, working closely with those in the device and medical fields, have made tremendous advances over the last 30 years. This article will focus on a number of these developments. We will also review the chemistry of the polymers, including synthesis and degradation, describe how properties can be controlled by proper synthetic controls such as copolymer composition, highlight special requirements for processing and handling, and discuss some of the commercial devices based on these materials.

POLYMER CHEMISTRY

Biodegradable polymers can be either natural or synthetic. In general, synthetic polymers offer greater advantages than natural materials in that they can be tailored to give a wider range of properties and more predictable lot-to-lot uniformity than can materials from natural sources. Synthetic polymers also represent a more reliable source of raw materials, one free from concerns of immunogenicity.

Polymer	Melting Point (°C)	Glass-Transition Temp (°C)	Modulus (Gpa)[a]	Degradation Time (months)[b]
PGA	225—230	35—40	7.0	6 to 12
LPLA	173—178	60—65	2.7	>24
DLPLA	Amorphous	55—60	1.9	12 to 16
PCL	58—63	(—65)— (—60)	0.4	>24
PDO	N/A	(—10)— 0	1.5	6 to 12
PGA-TMC	N/A	N/A	2.4	6 to 12
85/15 DLPLG	Amorphous	50—55	2.0	5 to 6
75/25 DLPLG	Amorphous	50—55	2.0	4 to 5
65/35 DLPLG	Amorphous	45—50	2.0	3 to 4
50/50 DLPLG	Amorphous	45—50	2.0	1 to 2
a Tensile or flexural modulus.				
b Time to complete mass loss. Rate also depends on part geometry.				

Table I. Properties of common biodegradable polymers.

The general criteria for selecting a polymer for use as a biomaterial is to match the mechanical properties and the time of degradation to the needs of the application (see Table I). The ideal polymer for a particular application would be configured so that it:

- Has mechanical properties that match the application, remaining sufficiently strong until the surrounding tissue has healed.
- Does not invoke an inflammatory or toxic response.
- Is metabolized in the body after fulfilling its purpose, leaving no trace.
- Is easily processable into the final product form.
- Demonstrates acceptable shelf life.
- Is easily sterilized.

The factors affecting the mechanical performance of biodegradable polymers are those that are well known to the polymer scientist, and include monomer selection, initiator selection, process conditions, and the presence of additives. These factors in turn influence the polymer's hydrophilicity, crystallinity, melt and glass-transition temperatures, molecular weight, molecular-weight distribution, end groups, sequence distribution (random versus blocky), and presence of residual monomer or additives. In addition, the polymer scientist working with biodegradable materials must evaluate each of these variables for its effect on biodegradation.[1]

Biodegradation has been accomplished by synthesizing polymers that have hydrolytically unstable linkages in the backbone. The most common chemical functional groups with this characteristic are esters, anhydrides, orthoesters, and amides. We will discuss the importance of the properties affecting biodegradation later in the article.

The following section presents an overview of the synthetic biodegradable polymers that are currently being used or investigated for use in wound closure (sutures, staples); orthopedic fixation devices (pins, rods, screws, tacks, ligaments); dental applications (guided tissue regeneration); cardiovascular applications (stents, grafts); and intestinal applications (anastomosis rings). Most of the commercially available biodegradable devices are polyesters composed of homopolymers or copolymers of glycolide and lactide. There are also devices made from copolymers of trimethylene carbonate and ε-caprolactone, and a suture product made from polydioxanone.

Polyglycolide (PGA). Polyglycolide is the simplest linear aliphatic polyester. PGA was used to develop the first totally synthetic absorbable suture, marketed as Dexon in the 1960s by Davis and Geck, Inc. (Danbury, CT). Glycolide monomer is synthesized from the dimerization of glycolic acid. Ring-opening polymerization yields high-molecular-weight materials, with approximately 1—3% residual monomer present (see Figure 1). PGA is highly crystalline (45—55%), with a high melting point (220—225°C) and a glass-transition temperature of 35—40°C. Because of its high degree of crystallization, it is not soluble in most organic solvents; the exceptions are highly fluorinated organics such as hexafluoroisopropanol. Fibers from PGA exhibit high strength and modulus and are too stiff to be used as sutures except in the form of braided material. Sutures of PGA lose about 50% of their strength after 2 weeks and 100% at 4 weeks, and are completely absorbed in 4—6 months. Glycolide has been copolymerized with other monomers to reduce the stiffness of the resulting fibers.

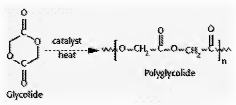


Figure 1. Synthesis of polyglycolide (PGA).

Polylactide (PLA). Lactide is the cyclic dimer of lactic acid that exists as two optical isomers, d and l. l-lactide is the naturally occurring isomer, and dl-lactide is the synthetic blend of d-lactide and l-lactide. The homopolymer of l-lactide (LPLA) is a semicrystalline polymer. These types of materials exhibit high tensile strength and low elongation, and consequently have a high modulus that makes them more suitable for load-bearing applications such as in orthopedic fixation and sutures. Poly(dl-lactide) (DLPLA) is an amorphous polymer exhibiting a random distribution of both isomeric forms of lactic acid, and accordingly is unable to arrange into an organized crystalline structure. This material has lower tensile strength, higher elongation, and a much more rapid degradation time, making it more attractive as a drug delivery system. Poly(l-lactide) is about 37% crystalline, with a melting point of 175—178°C and a glass-transition temperature of 60—65°C. The degradation time of LPLA is much slower than that of DLPLA, requiring more than 2 years to be completely absorbed. Copolymers of l-lactide and dl-lactide have been prepared to disrupt the crystallinity of l-lactide and accelerate the degradation process.

Poly(ε-caprolactone). The ring-opening polymerization of ε-caprolactone yields a semicrystalline polymer with a melting point of 59—64°C and a glass-transition temperature of —60°C (see Figure 2). The polymer has been regarded as tissue compatible and used as a biodegradable suture in Europe. Because the homopolymer has a degradation time on the order of 2 years, copolymers have been synthesized to accelerate the rate of bioabsorption. For example, copolymers of ε-caprolactone with dl-lactide have yielded materials with more-rapid degradation rates. A block copolymer of ε-caprolactone with glycolide, offering reduced stiffness compared with pure PGA, is being sold as a monofilament suture by Ethicon, Inc. (Somerville, NJ), under the trade name Monacryl.

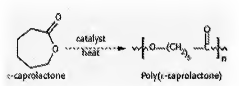


Figure 2. Synthesis of poly(ε-caprolactone).

Poly(dioxanone) (a polyether-ester). The ring-opening polymerization of *p*-dioxanone (see Figure 3) resulted in the first clinically tested monofilament synthetic suture, known as PDS (marketed by Ethicon). This material has approximately 55% crystallinity, with a glass-transition temperature of —10 to 0°C. The polymer should be processed at the lowest possible temperature to prevent depolymerization back to monomer. Poly(dioxanone) has demonstrated no acute or toxic effects on implantation. The monofilament loses 50% of its initial breaking strength after 3 weeks and is absorbed within 6 months, providing an advantage over Dexon or other products for slow-healing wounds.

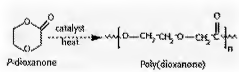


Figure 3. Synthesis of poly(dioxanone).ε-caprolactone).

Poly(lactide-co-glycolide). Using the polyglycolide and poly(l-lactide) properties as a starting point, it is possible to copolymerize the two monomers to extend the range of homopolymer

properties (see Figure 4). Copolymers of glycolide with both l-lactide and dl-lactide have been developed for both device and drug delivery applications. It is important to note that there is not a linear relationship between the copolymer composition and the mechanical and degradation properties of the materials. For example, a copolymer of 50% glycolide and 50% dl-lactide degrades faster than either homopolymer (see Figure 5). Copolymers of l-lactide with 25—70% glycolide are amorphous due to the disruption of the regularity of the polymer chain by the other monomer. A copolymer of 90% glycolide and 10% l-lactide was developed by Ethicon as an absorbable suture material under the trade name Vicryl. It absorbs within 3—4 months but has a slightly longer strength-retention time.

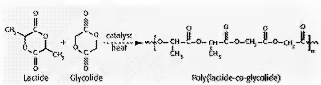


Figure 4. Synthesis of poly(lactide-co-glycolide). ε-caprolactone).

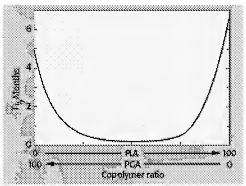


Figure 5. Half-life of PLA and PGA homopolymers and copolymers implanted in rat tissue. (Figure reproduced courtesy of Journal of Biomedical Materials Research, *11:711, 1977.)*

Copolymers of glycolide with trimethylene carbonate (TMC), called polyglyconate (see Figure 6), have been prepared as both sutures (Maxon, by Davis and Geck) and as tacks and screws (Acufex Microsurgical, Inc., Mansfield, MA). Typically, these are prepared as A-B-A block copolymers in a 2:1 glycolide:TMC ratio, with a glycolide-TMC center block (B) and pure glycolide end blocks (A). These materials have better flexibility than pure PGA and are absorbed in approximately 7 months. Glycolide has also been polymerized with TMC and *p*-dioxanone (Biosyn, by United States Surgical Corp., Norwalk, CT) to form a terpolymer suture that absorbs within 3—4 months and offers reduced stiffness compared with pure PGA fibers.

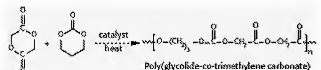


Figure 6. Synthesis of polyglyconate.

Other Polymers under Development. Currently, only devices made from homopolymers or copolymers of glycolide, lactide, caprolactone, p-dioxanone, and trimethylene carbonate have been cleared for marketing by FDA. A number of other polymers, however, are being investigated for use as materials for biodegradable devices.

In addition to their suitability for medical uses, biodegradable polymers make excellent candidates for packaging and other consumer applications. A number of companies are evaluating ways to make low-cost biodegradable polymers. One method is to bioengineer the synthesis of the polymers, using microorganisms to produce energy-storing polyesters. Two examples of these materials—polyhydroxybutyrate (PHB) and polyhydroxyvalerate (PHV)—are commercially available

as copolymers under the trade name Biopol (Monsanto Co., St. Louis) and have been studied for use in medical devices (see Figure 7). The PHB homopolymer is crystalline and brittle, whereas the copolymers of PHB with PHV are less crystalline, more flexible, and easier to process. These polymers typically require the presence of enzymes for biodegradation but can degrade in a range of environments and are under consideration for several biomedical applications.

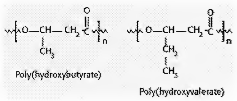


Figure 7. Molecular structure of two bioengineered polyesters that require specific enzymes for biodegradation.

The use of synthetic poly(amino acids) as polymers for biomedical devices would seem a logical choice, given their wide occurrence in nature. In practice, however, pure insoluble poly(amino acids) have found little utility because of their high crystallinity, which makes them difficult to process and results in relatively slow degradation. The antigenicity of polymers with more than three amino acids in the chain also makes them inappropriate for use in vivo. To circumvent these problems, modified "pseudo" poly(amino acids) have been synthesized by using a tyrosine derivative. Tyrosine-derived polycarbonates, for example, are high-strength materials that may be useful as orthopedic implants. It is also possible to copolymerize poly(amino acids) to modify their properties. The group that has been researched most extensively is the polyesteramides.

A Note on Nomenclature

A polymer is generally named based on the monomer it is synthesized from. For example, ethylene is used to produce poly(ethylene). For both glycolic acid and lactic acid, an intermediate cyclic dimer is prepared and purified, prior to polymerization. These dimers are called glycolide and lactide, respectively. Although most references in the literature refer to polyglycolide or poly (lactide), you will also find references to poly(glycolic acid) and poly(lactic acid). Poly(lactide) exists in two stereo forms, signified by d or l for dexorotary or levorotary, or by dl for the racemic mix.

The search for new candidate polymers for drug delivery may offer potential for medical device applications as well. In drug delivery, the formulation scientist is concerned not only with shelf-life stability of the drug but also with stability after implantation, when the drug may reside in the implant for 1—6 months or more. For drugs that are hydrolytically unstable, a polymer that absorbs water may be contraindicated, and researchers have begun evaluating more hydrophobic polymers that degrade by surface erosion rather than by bulk hydrolytic degradation. Two classes of these polymers are the polyanhydrides and the polyorthoesters.

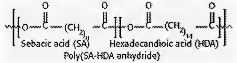


Figure 8. Molecular structure of poly(SA-HDA anhydride).

Polyanhydrides have been synthesized via the dehydration of diacid molecules by melt polycondensation (see Figure 8). Degradation times can be adjusted from days to years according to the degree of hydrophobicity of the monomer selected. The materials degrade primarily by

surface erosion and possess excellent in vivo compatibility. So far, they have only been approved for sale as a drug delivery system. The Gliadel product, designed for delivery of the chemotherapeutic agent BCNU in the brain, received regulatory clearance from FDA in 1996 and is being produced by Guilford Pharmaceuticals, Inc. (Baltimore).

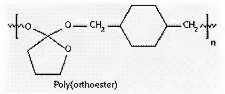


Figure 9. Molecular structure of poly(orthoester).

Polyorthoesters were first investigated in the 1970s by Alza Corp. (Palo Alto, CA) and SRI International (Menlo Park, CA) in a search for new synthetic biodegradable polymers for drug delivery applications (see Figure 9). These materials have gone through several generations of improvements in synthesis, and can now be polymerized at room temperature without forming condensation by-products. Polyorthoesters are hydrophobic, with hydrolytic linkages that are acid-sensitive but stable to base. They degrade by surface erosion, and degradation rates can be controlled by incorporation of acidic or basic excipients.

PACKAGING AND STERILIZATION

Because biodegradable polymers are hydrolytically unstable, the presence of moisture can degrade them in storage, during processing, and after device fabrication. In theory, the solution for hydrolysis instability is simple: eliminate the moisture and thus eliminate the degradation. However, because the materials are naturally hygroscopic, eliminating water and then keeping the polymer free of water are difficult to accomplish. The as-synthesized polymers have relatively low water contents, since any residual water in the monomer is used up in the polymerization reaction. The polymers are quickly packaged after manufacture—generally double-bagged under an inert atmosphere or vacuum. The bag material may be polymeric or foil, but it must be highly resistant to water permeability. To minimize the effects of any moisture present, the polymers are typically stored in a freezer. Packaged polymers should always be at room temperature when opened to minimize condensation, and should be handled as little as possible at ambient atmospheric conditions. As expected, there is a relationship among biodegradation rate, shelf stability, and polymer properties. For instance, the more hydrophilic glycolide polymers are much more sensitive to hydrolytic degradation than are polymers prepared from the more hydrophobic lactide.

Final packaging consists of placing the suture or device in an airtight, moistureproof container. A desiccant can be added to further reduce the effects of moisture. Sutures, for example, are wrapped around a specially dried paper holder that acts as a desiccant. In some cases, the finished device may be stored at subambient temperature as an added precaution against degradation.

Devices incorporating biodegradable polymers cannot be subjected to autoclaving, and must be sterilized by gamma or E-beam irradiation or by exposure to ethylene oxide (EtO) gas. There are certain disadvantages, however, to both irradiation and EtO sterilization. Irradiation, particularly at doses above 2 Mrd, can induce significant degradation of the polymer chain, resulting in reduced molecular weight as well as influencing final mechanical properties and degradation times. Polyglycolide, poly(lactide), and poly(dioxanone) are especially sensitive to ionizing radiation, and these materials are usually sterilized by EtO for device applications. Because the highly toxic EtO can present a safety hazard, great care must be taken to ensure that all the gas is removed from the device before final packaging. The temperature and humidity conditions should also be considered when submitting devices for sterilization. Temperatures must be kept below the glass-transition temperature of the polymer to prevent the part geometry from changing during

sterilization. If necessary, parts can be kept at 0°C or lower during the irradiation process.

PROCESSING

All commercially available biodegradable polymers can be melt processed by conventional means such as injection molding, compression molding, and extrusion. As with packaging, special consideration needs to be given to the exclusion of moisture from the material before melt processing to prevent hydrolytic degradation. Special care must be taken to dry the polymers before processing and to rigorously exclude humidity during processing.

Because most biodegradable polymers have been synthesized by ring-opening polymerization, a thermodynamic equilibrium exists between the forward or polymerization reaction and the reverse reaction that results in monomer formation. Excessively high processing temperatures may result in monomer formation during the molding or extrusion process. The presence of excess monomer can act as a plasticizer, changing the material's mechanical properties, and can catalyze the hydrolysis of the device, thus altering degradation kinetics. Therefore, these materials should be processed at the lowest temperatures possible.

Factors That Accelerate Polymer Degradation

- More hydrophilic backbone.
- More hydrophilic endgroups.
- More reactive hydrolytic groups in the backbone.
- Less crystallinity.
- More porosity.
- Smaller device size.

DEGRADATION

Once implanted, a biodegradable device should maintain its mechanical properties until it is no longer needed and then be absorbed and excreted by the body, leaving no trace. Simple chemical hydrolysis of the hydrolytically unstable backbone is the prevailing mechanism for the polymer's degradation. This occurs in two phases. In the first phase, water penetrates the bulk of the device, preferentially attacking the chemical bonds in the amorphous phase and converting long polymer chains into shorter water-soluble fragments. Because this occurs in the amorphous phase initially, there is a reduction in molecular weight without a loss in physical properties, since the device matrix is still held together by the crystalline regions. The reduction in molecular weight is soon followed by a reduction in physical properties, as water begins to fragment the device (see Figure 10). In the second phase, enzymatic attack and metabolization of the fragments occurs, resulting in a rapid loss of polymer mass. This type of degradation—when the rate at which water penetrates the device exceeds that at which the polymer is converted into water-soluble materials (resulting in erosion throughout the device)—is called bulk erosion. All of the commercially available synthetic devices and sutures degrade by bulk erosion.

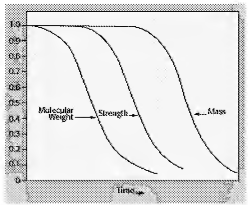


Figure 10. Generic absorption curves showing the sequence of polymer molecular weight, strength, and mass reduction. (Figure reproduced courtesy of Journal of Craniofacial Surgery, *(8)2:89, 1997.)*

A second type of biodegradation, known as surface erosion, occurs when the rate at which the polymer penetrates the device is slower than the rate of conversion of the polymer into water-soluble materials. Surface erosion results in the device thinning over time while maintaining its bulk integrity. Polyanhydrides and polyorthoesters are examples of materials that undergo this type of erosion—when the polymer is hydrophobic, but the chemical bonds are highly susceptible to hydrolysis. In general, this process is referred to in the literature as bioerosion rather than biodegradation.

- The degradation-absorption mechanism is the result of many interrelated factors, including:
- The chemical stability of the polymer backbone.
- The presence of catalysts, additives, impurities, or plasticizers.
- The geometry of the device.

Balancing these factors by tailoring an implant to slowly degrade and transfer stress at the appropriate rate to surrounding tissues as they heal is one of the major challenges facing researchers today.

COMMERCIAL BIODEGRADABLE DEVICES

The total U.S. revenues from commercial products developed from absorbable polymers in 1995 was estimated to be over $300 million, with more than 95% of revenues generated from the sale of bioabsorbable sutures. The other 5% is attributed to orthopedic fixation devices in the forms of pins, rods, and tacks; staples for wound closure; and dental applications.[2] Research into biodegradable systems continues to increase, from the 60 to 70 papers published each year in the late 1970s to the more than 400 each year in the early 1990s. The rate at which bioabsorbable fixation devices are cleared through the FDA 510(k) regulatory process is also increasing, with seven devices cleared for sale in 1995.

What follows is a brief overview of some of the significant commercial applications of biodegradable polymers.

Sutures. While comprising the lion's share of the total medical biodegradables market in 1995, this is a mature area not expected to grow rapidly in the future. About 125 million synthetic bioabsorbable sutures are sold each year in the United States. They are divided into braided and monofilament categories. Braided sutures are typically more pliable than monofilament and exhibit better knot security when the same type of knot is used. Monofilament sutures are more wiry and

may require a more secure knot. Their major advantage is that they exhibit less tissue drag, a characteristic that is especially important for cardiovascular, ophthalmic, and neurological surgeries. A recent source in the literature lists eight objective and three subjective parameters for suture selection based on criteria such as tensile strength, strength retention, knot security, tissue drag, infection potential, and ease of tying.[3]

Dental Devices. Biodegradable polymers have found use in two dental applications. Employed as a void filler following tooth extraction, porous polymer particles can be packed into the cavity to aid in quicker healing. As a guided-tissue-regeneration (GTR) membrane, films of biodegradable polymer can be positioned to exclude epithelial migration following periodontal surgery. The exclusion of epithelial cells allows the supporting, slower-growing tissue—including connective and ligament cells—to proliferate. Three examples of these GTR materials are Resolut from W.L. Gore (Flagstaff, AZ), Atrisorb from Atrix Laboratories (Fort Collins, CO), and Vicryl mesh from Ethicon.

Orthopedic Fixation Devices. Orthopedic fixation devices made from synthetic biodegradable polymers have advantages over metal implants in that they transfer stress over time to the damaged area, allowing healing of the tissues, and eliminate the need for a subsequent operation for implant removal. The currently available materials have not exhibited sufficient stiffness to be used as bone plates for support of long bones, such as the femur. Rather, they have found applications where lower-strength materials are sufficient: for example, as interference screws in the ankle, knee, and hand areas; as tacks and pins for ligament attachment and meniscal repair; as suture anchors; and as rods and pins for fracture fixation. Screws and plates of poly(l-lactide-co-glycolide) for craniomaxillofacial repair have recently been cleared for marketing in the United States under the trade name LactoSorb Craniomaxillofacial Fixation System (Biomet, Inc., Warsaw, IN).

Other Applications. Biodegradable polymers have found other applications that have been commercialized or are under investigation. Anastomosis rings have been developed as an alternative to suturing for intestinal resection. Tissue staples have also replaced sutures in certain procedures. Other applications currently under scrutiny include ligating clips, vascular grafts, stents, and tissue-engineering scaffolds. A list of commercial synthetic biodegradable polymer devices by category is given in Table II.

Application	Trade Name	Composition [a]	Manufacturer
	Dexon	PGA	Davis and Geck
	Maxon	PGA-TMC	Davis and Geck
	Vicryl	PGA-LPLA	Ethicon
Sutures	Monocryl	PGA-PCL	Ethicon
	PDS	PDO	Ethicon
	Polysorb	PGA-LPLA	U.S. Surgical
	Biosyn	PDO-PGA-TMC	U.S. Surgical
	PGA Suture	PGA	Lukens
	Sysorb	DLPLA	Synos

	Endofix	PGA-TMC or LPLA	Acufex
	Arthrex	LPLA	Arthrex
Interference screws	Bioscrew	LPLA	Linvatec
	Phusiline	LPLA-DLPLA	Phusis
	Biologically Quiet	PGA-DLPLA	Instrument Makar
Suture anchor	Bio-Statak	LPLA	Zimmer
	Suretac	PGA-TMC	Acufex
Anastomosis clip	Lactasorb	LPLA	Davis and Geck
Anastomosis ring	Valtrac	PGA	Davis and Geck
Dental	Drilac	DLPLA	THM Biomedical
Angioplastic plug	Angioseal	PGA-DLPLA	AHP
Screw	SmartScrew	LPLA	Bionx
Pins and rods	Biofix	LPLA or PGA	Bionx
	Resor-Pin	LPLA-DLPLA	Geistlich
Tack	SmartTack	LPLA	Bionx
Plates, mesh, screws	LactoSorb	PGA-LPLA	Lorenz
	Antrisorb	DLPLA	Atrix
Guided tissue	Resolut	PGA-DLPLA	W.L. Gore
	Guidor	DLPLA	Procordia

[a] Key to material composition:
DLPLA — poly(dl-lactide)
LPLA — poly(l-lactide)
PGA — polyglycolide
PDO — poly(dioxanone)
PGA-TMC — poly(glycolide-co-trimethylene carbonate)
PGA-LPLA — poly(l-lactide-co-glycolide)
PGA-DLPLA — poly(dl-lactide-co-glycolide)
LPLA-DLPLA — poly(l-lactide-co-dl-lactide)
PDO-PGA-TMC — poly(glycolide-co-trimethylene carbonate-co-dioxanone)

Table II. Some commercial biodegradable medical products.

Biodegradable Polymers in Tissue Engineering

One of the exciting current areas for applications of biodegradable polymers is in tissue engineering. Several companies are investigating using these materials as a matrix for living cells. Important properties in this regard include porosity for cell in-growth, a surface that balances hydrophilicity and hydrophobicity for cellular attachment, mechanical properties that are compatible with those of the tissue, and degradation rate and by-products. The polymer matrix may represent the device itself, or can be a scaffold for cell growth in vitro that is degraded by the growing cells prior to implantation. The device can also be formulated to contain additives or active agents for more rapid tissue growth or compatibility. For example, a bone implant may contain a form of calcium phosphate or a growth factor such as one of the bone morphogenetic proteins.

There are a number of ways of making the three-dimensional matrices required for tissue engineering. These methods include woven or nonwoven preparations from spun fibers, blown films using solvents or propellants, or sintered polymer particles. One of the newest methods is being developed by Therics (Princeton, NJ), which has licensed a system for building three-dimensional devices for use as scaffolds and in drug delivery products. In this system, small spheres of polymer are laid out in thin films. Using technology similar to that found in ink-jet printers, small amounts of solvent are used to fuse particles together. The particles not fused are removed and another layer of particles laid out. This particle placement and fusing is continued for many layers, until the exact three-dimensional structure is obtained. Because each polymer layer is applied in a separate step, different polymers can be used to obtain different properties in the interior and exterior of the device.

CONCLUSION

We have attempted to provide an overview of the medical device uses of biodegradable polymers. While sutures were the first commercial product and still account for the vast majority of all sales, a variety of products are now on the market for an expanding range of applications, with others certain to appear in the next decade.

What is it about these materials that makes them so attractive to the device industry? First, in this conservative field, where devices serve critical, perhaps life-and-death, functions, the industry is slow to accept new materials or new designs. The polymers prepared from these materials, particularly lactide and glycolide, have a long history of safe and effective use. Building on this solid foundation, researchers will continue to evaluate these materials, taking advantage of the wide range of properties that can be obtained in polymers built with relatively few monomer units. We expect that, in the future even more than today, device designers and physicians will have available a wealth of products using biodegradable polymers that will help speed patient recovery and eliminate follow-up surgeries.

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